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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,383	10/27/2003	Ekambar R. Kandimalla	HYB-005US4	5766

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EXAMINER	
HORNING, MICHELLE S	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,383	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14-19,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 14, 39, 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to communication filed 5/18/2009. The status of the claims is as follows: claims 12, 14, 39 and 40 are under current examination and claims 15-19 are withdrawn.

Of note, the original elected species is Oligo #2 or SEQ ID NO: 2 as disclosed by the instant application in Example 2. This species is CTATCTGAC*GTTCTCTGT wherein C* represents 5-hydroxycytosine (Remarks, 5/10/2007) and this no longer reads upon the claims.

Any rejection(s) not reiterated herein has been withdrawn.

Claim Rejections - 35 USC § 102-NECESSITATED BY AMENDMENTS

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Cook (US Patent No. 5599797) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993).

Cook discloses phosphorothioate oligonucleotide sequences joined together by all phosphorothioate linkages (see abstract, SEQ ID NO: 1). The phosphorothioate oligonucleotide CCTTTCGCGACCCACACTA (SEQ ID NO: 1, col. 12, lines 55+) is an immunostimulatory oligonucleotide compound comprising a sequence of formula:

5'-Um……U1-X1-X2-Y-Z-X3-X4-D1……Dm-3'

Wherein:

Y is a non-natural pyrimidine nucleoside (see underlined C above);

Z is a non-natural purine nucleoside (see underlined G above);

Wherein the flanking X2 and X3 of CG are immunostimulatory moieties;

wherein the immunostimulatory moiety is a 1', 2'-dideoxyribose (see Figure 3 of the instant specification, providing the structure of 1', 2'-dideoxyribose or a phophorothioate linkage as shown in Fig. 1 in the Stein and Cheng reference);

and wherein at least one X, U, or D is an immunostimulatory moiety.

Cook describes oligonucleotides comprising phosphorothioates as exhibiting resistance to nucleases and generally more chemically stable than natural phosphodiester oligonucleotides (col. 2, lines 56+). Note that this meets the definition of an "immunostimulatory moiety" as defined by the instant specification [0065]. The definition provides that an immunostimulatory moiety is a structure that causes the immunostimulatory oligonucleotide to be more immunostimulatory than it would be in the absence of the immunostimulatory moiety. The phosphorothioate-containing oligonucleotide is more immunostimulatory in that the phosphorothioate would lead to a more stable structure allowing it to perform its structure-dependent immunostimulatory function as opposed to one lacking the phosphorothioate which would lead to nuclease-dependent degradation.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Weiner et al. (*PNAS*, 1997) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993).

Weiner et al. discloses the immunostimulatory oligonucleotide TCTCCCAGCGTGCGCCAT which comprises 2 CpG motifs (ODN 1758, Table 1, p. 10834). This immunostimulatory oligonucleotide comprises the formula,

5'.....U3-U2-U1-X1-X2-Y-Z-X3-X4-D1-D2-D3...Dm-3'

Wherein Y is a non-natural pyrmidine nucleoside (see 1st CG);

Z is a guanosine;

Wherein X3, X4 and D1 are naturally occurring nucleosides (see TGC);

Wherein D2 is an immunostimulatory moiety;

wherein the immunostimulatory moiety is a 1', 2'-dideoxyribose (see Figure 3 of the instant specification providing the structure of 1', 2'-dideoxyribose or a phophorothioate linkage as shown in Fig. 1 in the Stein and Cheng reference);

and wherein at least one of X, U or D is an immunostimulatory moiety.

Note that Weiner et al. characterize the immune responses to both the sequence above (ODN 1758) and a control sequence which lacks unmethylated CpG motifs (ODN 1812, Table 1, p. 10834). The author describe that there is minimal immunostimulatory effects following administration of the control sequence (Table 1, p. 10834). Note that this meets the definition of an "immunostimulatory moiety" as defined by the instant specification [0065]. The definition provides that an immunostimulatory moiety is a

structure that causes the immunostimulatory oligonucleotide to be more immunostimulatory than it would be in the absence of the immunostimulatory moiety.

Claim Rejections - 35 USC § 103-NECESSITATED BY AMENDMENTS

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (US Patent No. 5599797) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993).

As discussed above, the teachings by Cook provide an oligonucleotide compound comprising a sequence of CCTTTCGCGACCCACACTA and conforming to the formula:

5'-Um……U1-X1-X2-Y-Z-X3-X4-D1……Dm-3'

Wherein:

Y is a non-natural pyrimidine nucleoside (see underlined C above);

Z is a non-natural purine nucleoside (see underlined G above);

Wherein the flanking X2 and X3 of CG are immunostimulatory moieties;

wherein the immunostimulatory moiety is a 1', 2'-dideoxyribose (see Figure 3 of the instant specification, providing the structure of 1', 2'-dideoxyribose or a phophorothioate linkage as shown in Fig. 1 in the Stein and Cheng reference);

and wherein at least one X, U, or D is an immunostimulatory moiety.

Cook does not disclose a specific sequence comprising a 4-thiouracil.

Cook describes generally incorporating modified bases including a 4-thiouracil in the phosphorothioate oligonucleotides to increase their nuclease resistance in order to facilitate their use as therapeutic reagents (col. 7, lines 45+ and instant claim 39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings by Cook and further incorporate a 4-thiouracil into the sequence CCTTTCGCGACCCACACTA (SEQ ID NO: 1). One of ordinary skill in the art at the time the invention was made would have been motivated to do so in order to increase its nuclease resistance and to facilitate its use as therapeutic reagents. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques and methods are widely used and commonly known. The invention as a whole was *prima face* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 14 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner et al. (*PNAS*, 1997) in further view of Cook (US Patent No. 5599797) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993).

As discussed above, Weiner et al. discloses the immunostimulatory oligonucleotide TCTCCCAGCGTGCGCCAT which comprises 2 CpG motifs (ODN 1758, Table 1, p. 10834). This immunostimulatory oligonucleotide comprises the formula,

5'……U3-U2-U1-X1-X2-Y-Z-X3-X4-D1-D2-D3…Dm-3'

Wherein Y is a non-natural pyrmidine nucleoside (see 1st CG);

Z is a guanosine;

Wherein X3, X4 and D1 are naturally occurring nucleosides (see TGC);

Wherein D2 is an immunostimulatory moiety;

wherein the immunostimulatory moiety is a 1', 2'-dideoxyribose (see Figure 3 of the instant specification providing the structure of 1', 2'-dideoxyribose or a phophorothioate linkage as shown in Fig. 1 in the Stein and Cheng reference);

and wherein at least one of X, U or D is an immunostimulatory moiety.

Weiner et al. does not disclose incorporating a 4-thiouracil in immunostimulatory oligonucleotides.

Cook describes generally incorporating modified bases including a 4-thiouracil in the phosphorothioate oligonucleotides to increase their nuclease resistance in order to facilitate their use as therapeutic reagents (col. 7, lines 45+ and instant claim 39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings by Weiner et al. and Cook and further incorporate a 4-thiouracil into the sequence TCTCCCAGCGTGCGCCAT (ODN 1758). One of ordinary skill in the art at the time the invention was made would have been motivated to do so in order to increase its nuclease resistance and to facilitate its use as therapeutic reagents. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques and methods are widely used and commonly known. The invention as a whole was *prima face* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting-MAINTAINED

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12, 14, 39 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 10/865, 245. Although the conflicting claims are not identical, they are not patentably distinct from each other because other because both sets of claims are directed to an immunostimulatory oligonucleotide containing a CpG as well as linkers. Further, both sets of claims are very broad in scope in that they overlap in common oligonucleotides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 12, 14, 39 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of copending Application No. 10/694, 418. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to an immunostimulatory oligonucleotide containing a CpG, immunostimulatory moiety including a C3 alkyl linker, 4-thiouracil and a nucleoside methylphosphonate. Further, both sets of claims are very broad in scope and they are both drawn to comparable sequence structures.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 12, 14, 39 and 40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7262286. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an immunostimulatory oligonucleotide containing a CpG formula and in which the C is an analog, including 4-thiouracil. Because both sets are broad in scope, they are both drawn to similar sequence structures.

Response to Arguments

In response to the rejection(s), Applicant submits that the copending application has a later filing date. This has been noted, however, until the rejection is properly addressed, it is maintained on the record. Note that Applicant argues that the claims of Patent No. 7262286 do not teach any of the positional modifications of claims 12 and 14. This is incorrect both sets of claims are drawn to a phosphorothioate or a 1', 2'-dideoxyribose (see Figure 3 of instant specification and Fig. 1 in the Stein and Cheng reference). Also note that new claims 39 and 40 are drawn to a 4-thiouracil.

Conclusion

No claim is allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/M. H./
Examiner, Art Unit 1648